Applicants have obviated the Examiner's comments with respect to the use of trademarks in the specification.

The objections to claims 15, 18 and 25 have been obviated by the amendments to the specification.

Claims 15-26 were rejected under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit that the Examiner's acknowledgment that the claims are enabling for *in vitro* uses should put an end to the inquiry. The law is clear that if claims are enabled for one use, no further inquiry is needed.

Even turning to the Examiner's specific objections with respect to the *in vivo* use of the present invention, applicants respectfully disagree.

The references relied upon by the Examiner do not go to whether or not the method claimed works. Rather, the references go to the issue of whether or not gene therapy has demonstrated **clinical efficacy**. However, the U.S. Court of Appeals for the Federal Circuit has explicitly held that such clinical efficacy is not the appropriate standard to be used by the PTO. In *In Re Brana*, 51 F.3d 1560, 1567, 34 U.S.P.Q. 2d 1436, 1443 (Fed. Cir. 1995) the Court explicitly cautioned the PTO with confusing its role with that of the FDA stating:

> The Commissioner counters that such in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means in vivo testing in humans, and therefore are not reasonably predictive of the success of the humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. **The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patient with the requirements for obtaining government approval to market a particular drug for human consumption.** See Scott v. Finney, 34 F.3d 1058, 1063, 32 U.S.P. 2d (BNA) 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings."). [Emphasis added].

Applicants submit that the references cited, which go to clinical efficacy is simply not relevant to what is claimed. And, if the references have any relevance, they confirm that a wide range of vectors such as those claimed herein effectively deliver genes to cells *in vivo*.

Moreover, contrary to the Examiner's statement that applicants have not demonstrated any method of targeting the malignant cells *in vivo*, applicants respectfully disagree. Applicants have provided three separate *in vivo* tests beginning at page 26-36 of the specification. Thus, applicants used the established rat glioma model and administered a marker gene, βgal under the control of an E2F responsive promoter or the CMV promoter to normal and malignant cell. The results are in Figures 3 and 4. These show that when the gene was administered under the control of the CMV promoter, it resulted in expression in both normal and malignant tissues. However, placing the gene under the control of an E2F responsive promoter resulted in virtually no staining in the normal tissues, but extensive staining in the malignant tissues. (See specifically Figures 3C and 3D and pages 31 and 32). Figure 4 shows a second test with administering the marker to the liver.

Yet another test is shown in Figure 5 where a therapeutic gene, the Herpes TK gene, is used. Whereas administration of the gene under the control of the CMV promoter resulted in extensive areas of local brain necrosis, inflammation and hemorrhage, the same gene under the control of E2F responsive promoter resulted in no obvious normal tissue toxicity (see specifically pages 34-36).

Accordingly, applicants respectfully submit that far from providing no *in vivo* data, they provided extensive *in vivo* data establishing that the invention works as claimed.

Moreover, when the Examiner talks about issues concerning difficulties arising from immune response, transient expression, etc., they certainly do not apply to claims such as claims 19-24 which are directed to use of genes that need only be expressed for a short term. Thus, as shown, for example, applicants have demonstrated that using a gene such as the TK gene (specifically claimed in claim 22), one only needs transient short-term expression. Similarly, when expressing a toxin, one only needs small amounts expressed and short-term expression of such genes.

Accordingly, applicants submit that this rejection of the claims should be withdrawn.

Claims 15-26 were rejected under 35 U.S.C. § 112 , second paragraph.

Applicants respectfully submit that the amendments to the claim have obviated most of the Examiner's objections. With respect to the Examiner's objections regarding the term "dominate negative mutant", applicants have the following comments.

The phrase "dominate negative mutant" is a well-known term. Applicants are submitting two pages from a "Google" search using that term, which showed 9,650 hits for that phrase establishing the widespread acceptance as to what this term meant. Thus, applicants respectfully submit that the rejection of claim 20 should be withdrawn.

In view of the other amendments, applicants submit that all rejections of the claims under 35 U.S.C. § 112 should be withdrawn.

Claims 15, 25 and 26 were rejected under 35 U.S.C. § 102(a), as being anticipated by U.S. Patent No. 5,885,833 ('833).

Applicants respectfully submit that this rejection of the claims should be withdrawn.

Applicants taught that one of the problems frequently seen in targeting malignant cells with various therapies, is that it is difficult to selectively target such cells. The present claim is directed to a method that **selectively targets cells** by **selectively expressing** a gene in a malignant cell. Applicants have done this by their discovery that using an E2F responsive promoter can result in expression of a gene in selective cells. Such a method is in no way taught by the '833 patent. The '833 patent does not have a step such as claim 25 of determining whether a malignant cell expresses sufficient levels of E2F to cause expression of a gene operably linked to E2F responsive promoter. Rather, that patent seeks to take advantage of E2F's effect in cell cycling. However, as explained in the present specification, the selectivity applicants have found and demonstrated is all the more remarkable, because E2F is normally expressed in a cell cycle dependent manner (see paragraph bridging pages 7 and 8). Thus, one would not expect such selectivity and the present method would not be obvious.

Accordingly, applicants respectfully submit that this rejection of the claims should be withdrawn.

Claims 15-23 and 25-26 were rejected under 35 U.S.C. § 103(a) has been unpatentable over *Raj et al.* or *Xiao et al.* or U.S. Patent No. 5980085833 in view of WO 94/18992 and U.S. Patent No. 5,529,774.

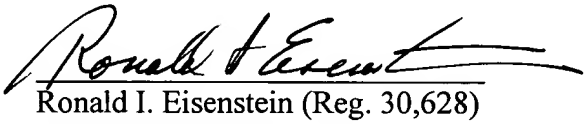
Applicant respectfully submit that this rejection should be withdrawn for the following reasons:

As discussed above, the present method is directed to a method that takes advantage of applicants' discovery that while E2F is normally expressed in a cell cycle dependent manner in all cells, the high levels expressed in malignant cells results in the selective expression of genes

under the control of an E2F responsive promoter. Thus, applicants not only showed expression of an E2F responsive promoter linked gene in a malignant cell, but also showed selective expression. See the examples discussed above and shown in Figures 3, 4 and 5. This is very important, as shown at pages 34-36, because when one uses a TK gene under a promoter such as a CMV promoter, one sees a negative effect from that expression on normal cells. In contrast, when one uses an E2F responsive promoter, the normal cells show virtually no negative effect. There is nothing in any of references that in any way suggest that such selective expression could be accomplished. Accordingly, applicants respectfully submit that this rejection of the claims should be withdrawn.

In view of the foregoing, applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,



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